Original Article

Steroid Response Rate in Childhood Nephrotic Syndrome at a Tertiary Hospital in South-Eastern Nigeria

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Abstract

Background: Response to corticosteroids in childhood nephrotic syndrome (NS) remains the best prognostic marker of the disease. African children have been noted to respond poorly to corticosteroids. However, recent reports in some parts of Nigeria suggest high steroid responsiveness. **Objectives:** This study was done to determine the steroid response rate and associated clinical variables among children with NS in Umuahia, South-Eastern Nigeria. **Patients and Methods:** A retrospective, descriptive study of all the children managed for NS from June 2013 to June 2018 was retrieved and relevant information obtained. Data analysis was done using the SPSS software version 20.0 for Windows® (IBM SPSS Inc. 2011 Chicago, Illinois, USA). **Results:** A total of 30 children aged 2 years to 15 years with a median of 8 years were studied. Male-to-female ratio was 2:1. Fifteen patients achieved remission with steroid with remission rates of 50% overall and 62.5% among children with idiopathic NS. Patients that achieved remission had a lower mean age (mean difference = -5.13, confidence interval [CI] −7.73, −2.54; $P < 0.001$) compared to those that had steroid resistance. The frequency of steroid resistance in males was not different from females (odd ratio = 1, CI = 0.22–4.56; $\chi^2 = 0.00$ $P = 1.00$). Children aged 5 years and below had the highest remission rate, whereas those above the age of 10 years were all steroid resistant. There was no significant mean difference in the levels of serum albumin and total cholesterol among the children who achieved remission compared to nonresponders. Frequencies of hematuria, hypertension, and raised serum creatinine were not significantly different between the two groups. **Conclusions:** About two-thirds of children with idiopathic NS in our center achieve complete remission with steroid therapy, whereas about one-third have steroid resistance which predominates after the age of 10 years. Frequency of some clinical variables such as hematuria, hypertension, and raised serum creatinine did not significantly differ among steroid responders compared to nonresponders.

Keywords: Child, nephrotic syndrome, Nigeria, remission induction, steroids

Introduction

Nephrotic syndrome (NS) is the most common manifestation of glomerular disease in childhood and a leading cause of chronic kidney disease among the pediatric age group.[1,2] In Nigeria, it accounts for 20%–48% of pediatric renal admissions.[3-6] About 85%–90% of the children with NS have the idiopathic form with varied degrees of responses to steroid therapy.[1] Initial response rate of 90%–95% has been reported among Caucasian children with steroid-sensitive NS, yet relapse occurs in about 60%–90%.[7]

The use of prednisolone for children with NS dates back to the 1950s and currently remains the mainstay for the initial treatment of NS.[8] Steroid responsiveness which is the most important determinant of the outcome and a vital classification pattern of NS is known to vary among ethnic groups, geographical location, and age at onset.[2,9,10]

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Steroid-sensitive NS has a better prognosis with preservation of long-term renal function and thus lower risk of developing end-stage renal disease.[11] The minimal change nephropathy has been reported as the most common cause of NS in children with over 80% responsiveness to steroids.[1] Most times, in our setting, the cause of NS may not readily be ascertained due to unavailability of diagnostic services such as renal biopsy and histology. However, some studies have suggested that some factors such as hematuria and hypertension when present may

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influence the patient's responsiveness to steroids.[11-13] No study has been done to ascertain how some of these factors influence steroid responsiveness in our locality.

This study was, therefore, carried out to determine the steroid response rate among children with NS in Umuahia, South-eastern Nigeria. It also sought to identify the clinical variables associated with steroid responsiveness among these children. This may help to categorize patients that may likely respond to steroid at presentation even when renal histology is unavailable. It will also serve as a guide to counsel the patients and their caregivers on treatment options.

Patients and Methods

This was a retrospective study of all children admitted and managed for NS over a 5-year period (June 2013 to June 2018) in the Pediatric Nephrology Unit of Federal Medical Center, Umuahia. The hospital serves the people of Abia state and also provides health services to adjoining communities of boundary states of Imo and Akwa Ibom. Before commencing the study, ethical approval was sought and obtained from the Health Research Ethics Committee of the hospital. Using the pediatric nephrology register, the cases with the diagnosis of NS were selected for the study. The case records of the children were retrieved from the medical records department. Information on relevant patient characteristics such as age, sex, clinical, and laboratory parameters as well as response to steroid was retrieved. The social class of each child was calculated based on the parents' level of education and occupation using Oyedeji's classification.[14]

Definition of terms

NS was defined as the presence of heavy proteinuria (urine dipstick ≥3+ or urine protein creatinine ratio of >2.0), hypoalbuminemia (serum albumin <2.5 g/100 ml), and edema.[1] Urinary tract infection was defined as the growth of 100,000 or more colony-forming units of a single organism per milliliter of a midstream/clean catch urine sample.[15] Hypertension was defined as systolic or diastolic blood pressure levels >95th percentile for age, gender, and height.[16] The patients were classified as idiopathic NS when no clinical or laboratory feature specific for a secondary cause was identified and as secondary NS if a secondary cause was identified.[1] Remission was defined as negative or trace proteinuria on dipstick urinalysis for 3 consecutive days.[1]

Treatment protocol

All the patients with NS studied were commenced on daily oral prednisolone at 60 mg/m^2 for 6 weeks. If they failed to achieve remission within 6 weeks of therapy, they were allowed 2 extra weeks for possible response. If they failed to achieve remission within 8 weeks of daily corticosteroid therapy, they were considered steroid resistant. Those who were steroid resistant were treated with calcineurin inhibitor (either cyclosporine or tacrolimus) after obtaining a kidney biopsy in those that gave consent. For those who achieved remission, after 6 weeks of daily prednisolone, they were changed to 40 mg/m^2 as alternate day regimen for 4 weeks after which the prednisolone was tapered over the next 3 months and discontinued.

Ethical issues

Ethical approval (FMC/QEH/G.596/Vol. 10/391) was procured from the Health Research and Ethics Committee of the hospital.

Data analysis plan

Data were cleaned, coded, and entered into the computer. Analysis was done using the Statistical Package for the Social Sciences (SPSS) software version 20.0 for Windows® (IBM SPSS Inc. 2011 Chicago, Illinois, USA). Data were checked for completeness and cases with missing records were excluded from the analysis. Descriptive statistics such as mean, median, and standard deviation were used to analyze the continuous variables. Differences in means were compared using the Student's *t*-test. Frequencies and percentages of categorical variables were determined. Pearson Chi-square and Fisher's exact tests were used to test for the clinical and laboratory variables associated with steroid response. Confidence interval (CI) was calculated at 95% level, and significant level was set at $P < 0.05$.

Results

General characteristics of the participants

There were 35 patients with the diagnosis of NS out of 1844 hospital admissions. Of these 35, five were excluded due to loss to follow-up before steroid sensitivity pattern could be established. Of the 30 patients that were analyzed, 20 (66.7%) were male, with a male-to-female ratio of 2:1. Their ages at first presentation ranged from 2 years to 15 years with a median age of 8 years. The mean age was 7.83 ± 4.29 years. Mean serum albumin was 2.348 ± 1.033 g/dl, whereas the mean total cholesterol was 363.37 ± 110.54 mg/dl. Hypertension occurred in 56% of the patients. Hematuria and urinary tract infection occurred in 53.8% and 28.6% of the patients, respectively. Of the 30 patients, 27 had their serum creatinine values available. Majority of the patients (22/27 [81.5%]) had normal serum creatinine values. Eighty percent of the patients (24/30) were classified as idiopathic due to nonidentification of a secondary cause both clinically and from laboratory tests. The secondary causes were found in six patients as follows: Glomerulonephritis (4), human immunodeficiency virus (1), and systemic lupus erythematosus (1). Table 1 shows the sociodemographic characteristics of all children with NS.

Steroid response rate and clinical parameters

Of the 30 patients, half achieved remission and half did not achieve remission. Remission rate was 50% (15/30) overall and 62.5% (15/24) among those with idiopathic NS. Steroid resistance was found in 50% (15/30) of all patients and in 37.5% (9/24) of those with idiopathic NS. None of the six patients identified as secondary NS achieved remission. Ten (50%) of the 20 males achieved remission, whereas 5 (50%) of the ten females also achieved remission. There was no gender difference in the response to steroid (odd ratio = 1,

CI = 0.22–4.56; χ^2 = 0.00; *P* = 1.00). The mean age of patients that achieved remission was 5.27 ± 2.549, whereas the mean age of patients with steroid resistance was 10.40 ± 4.188 (*t* = −4.055, *P* < 0.001). Table 2 shows the steroid response across the various age groups with children aged 5 years and below having the highest remission rate. All the children above 10 years of age did not achieve remission.

Table 3 shows a comparison of variables between the children that achieved remission and those that did not achieve remission. Children who achieved remission were younger in age (mean difference = −5.13, [CI −7.73, −2.54]; *P* < 0.001). Although not statistically significant, higher levels of serum total cholesterol as well as higher rate of hematuria were observed among the children who did not achieve remission.

Five out of 9 children with steroid-resistant idiopathic NS had renal biopsies while four children declined consent for renal biopsy due to cost. The histological types found among those that had renal biopsies were: Focal segmental glomerulosclerosis (FSGS) in four and membranoproliferative glomerulonephritis (MPGN) in one. Biopsy was not done for children with the secondary causes of NS.

Table 1: Sociodemographic characteristics of all the children with nephrotic syndrome

Variable	Frequency (%)**
Age group (years)	*n*=30*
≤5	11 (36.7)
6-10	10 (33.3)
>10	9 (30.0)
Sex	*n*=30*
Male	20 (66.7)
Female	10 (33.3)
Social class	*n*=29*
Upper	11 (37.9)
Middle	12 (41.4)
Lower	6 (20.7)

*The number of cases with information on the variable, **Percentages are of the total in each group

Table 2: Steroid response rate across the various age groups

Age group (years)	Achieved remission, *n* (%)	No remission, *n* (%)	Total
≤5	8 (72.7)	3 (37.5)	11
6-10	7 (70.0)	3 (30.0)	10
>10	0 (0.0)	9 (100.0)	9
Total	15 (50)	15 (50)	30 (100)

χ^2=12.87, *P*=0.002

Discussion

Studies within and outside Nigeria have shown variable responses to steroid among children with NS.[11-13,17-19] Our findings of 50% steroid responsiveness among all the participants with NS and 62.5% among those with idiopathic NS show that up to half of all the children with NS in our center are steroid resistant while among those with idiopathic NS, up to one-third are steroid resistant. These figures are comparable to the steroid response rates ranging from 45.2% to 65% observed by most of the earlier studies in Africa.[18-22] However, some studies in Port Harcourt,[23] Abuja,[24] and Lagos[13] Nigeria as well as in Nepal[25] documented higher steroid response rates of 80%, 73.9%, 75.9%, and 93.75%, respectively. On the other hand, remarkably lower steroid responses were reported by Adedoyin *et al*. in Ilorin (17.9%)[26] and Okoro and Okafor in Enugu (30%).[27] The variations observed across the studies may be explained by multiple factors such as differences in genetic makeup, age at presentation, predominant histologic type, and/or environmental factors. Although these variations exist, current researchers are postulating that the incidence of steroid resistance might be decreasing worldwide.[13,28] In our center, however, the rate of steroid resistance is still high, and this may suggest additional diagnostic services and use of second-line drugs with the attendant cost implications.

The higher mean age of children with steroid resistance compared to those who achieved remission with steroid was reported by other authors,[11,13,24] revealing that with older age at onset, the risk of steroid resistance increases. Gulati *et al*.[29] in India reported steroid resistance to be more likely in children

Table 3: Comparison of variables among children who achieved remission and those with steroid resistance

Variable	Achieved remission (steroid sensitive)	No remission (steroid resistant)	Mean difference (95% CI)	*P*
Mean age (years)	5.27±2.5	10.40±4.1	−5.13 (−7.73-−2.54)	<0.001
Mean serum albumin (g/dl)	2.2±1.0	2.5±1.1	−0.38 (−1.2-0.46)	0.358
Mean serum cholesterol (mg/dl)	347.2±106.9	381.0±116.9	−33.79 (−130.8-63.2)	0.477
Variable	**Achieved remission (steroid sensitive) (%)**	**No remission (steroid resistant) (%)**	**OR (95% CI)**	***P***
Hypertension (25)*	7/12 (58.3)	7/13 (53.8)	1.2 (0.2-5.8)	0.821
Hematuria (26)*	6/13 (46.2)	8/13 (61.5)	0.5 (0.1-2.6)	0.431
Raised serum creatinine (27)*	3/14 (21.4)	2/13 (15.4)	1.5 (0.2-10.8)	>0.999
UTI (21)*	3/11 (27.3)	3/10 (30.0)	0.9 (0.1-5.8)	>0.999

*The number of patients with information on the variable. Percentages represent proportion of the total within the group. UTI: Urinary tract infection, OR: Odds ratio, CI: Confidence interval

aged 8 years and above. In Ibadan Nigeria, older children did as well as those <6 years of age. Furthermore, while many studies have observed a male preponderance in NS,[6,11,18,19,25,30-32] the effect of gender on steroid responsiveness is not clear. Gulati *et al*.[29] reported the male sex as a predictor of resistance to steroid, but this was not so for Mortazavi and Khiavi[11] who observed that girls had significant resistance to steroids. Asinobi *et al*.[21] in Ibadan reported that boys were more likely to be steroid-sensitive than girls. In our study, however, there was no gender difference in steroid response rates.

Frequency of hypertension was not significantly different in the steroid responders compared to steroid nonresponders in our study. This however differs from the report by Davutoglu *et al*. in Turkey[12] who found that hypertension was a significant factor associated with nonresponse to steroids having observed that only about 4.2% of steroid responders were hypertensive at admission as against 26.4% of nonresponders who were hypertensive at presentation. Mortazavi and Khiavi in Iran[11] and Ladapo *et al*. in Lagos Nigeria[13] also observed that hypertension was significantly more prevalent in the nonsteroid responders. Contrary to the earlier thoughts that children with NS have normal or low blood pressure, recent findings allude to the fact that significant number of children with NS do have hypertension.[33] Among children with idiopathic NS, 10%–35% will have hypertension depending on the histologic type.[1]

In our study, there was no significant difference in the frequency of hematuria among those who achieved remission compared to those with steroid resistance. This is in contrast to the study by Mortazavi and Khiavi who observed the frequency of hematuria as a presenting feature to be significantly more amongst steroid resistant compared to steroid sensitive NS.[11] In Lagos, Ladapo *et al*. found a higher frequency of hematuria among children with steroid resistance.[13] Majority (80%–90%) of children with minimal change NS (MCNS) respond to steroid therapy.[1] While hematuria has been documented as one of the features that make MCNS less likely, and hence, a higher likelihood of steroid resistance; still, up to 20% of children with MCNS still experience hematuria.[1]

The mean serum albumin did not influence steroid responsiveness in our study as was also observed by Ladapo *et al*. in Lagos.[13] Serum cholesterol was also observed not to influence steroid responsiveness in our study. This is in contrast with what was documented by Ladapo *et al*.[13] in Lagos where serum cholesterol was significantly higher among those with steroid resistant NS. The smaller sample size used in our study may have constrained us from having a clearer picture of the contribution of these factors to steroid response.

Earlier studies have reported varied histopathological patterns among children with NS.[13,18,20,21,23,27] However, the indications for renal biopsies in most of the Nigerian studies[13,31] as well as in our study were resistance/non responsiveness to steroids and/or atypical presentation. This therefore may explain our predominant histologic finding of FSGS as in other Nigerian studies.[13,23,32] It is usually believed that most of the steroid responsive cases will be of the minimal change histologic type and most times renal biopsies are reserved for nonsteroid responders. Olowu *et al*.[20] observed MPGN as the most prevalent histologic type and closely followed by FSGS. Although it may be argued that there is no unique pattern from most of the African studies, FSGS seemingly ranks as a frequent cause of SRNS in the African child.

Limitations

The retrospective nature of this study as well as the small sample size may have affected the true rate of steroid response in our locality. Our hospital is a referral center and may have missed some of the cases of childhood NS who did not access the hospital. However, the cases seen and managed will still represent a pattern in the environment.

Conclusions and Recommendation

About two-thirds of children with idiopathic NS in our center achieve complete remission following steroid therapy while about one-third have steroid resistance which predominates after the age of 10 years. The frequency of some clinical variables such as hematuria, hypertension, and raised serum creatinine did not significantly differ among steroid responders compared to nonresponders. Hence, children with NS who present with such features in our setting where renal biopsy is not readily offered should be offered corticosteroid therapy until steroid resistance is established.

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Conflicts of interest

There are no conflicts of interest.

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